IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 19215US02

In the Application of:

Mark F. Pittenger, et al.

Serial No.: 10/690,435

Filed: 10/21/2003

For: Cardiac Muscle Regeneration Using Mesenchymal Stem Cells

Examiner: Fereydoun G. Sajjadi

Group Art Unit: 1633

Confirmation No.: 3718

Filed via Electronic Filing on April 25, 2008

AMENDMENTS TO BRIEF ON APPEAL

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Dear Sirs:

This communication is being submitted in response to the Notification of Non-Compliant Appeal Brief mailed on April 14, 2008. This response is timely because it is filed within one month of the mailing date of the Notification.

Applicants hereby submit an entire amended appeal brief to correct the sections identified as defective in the Notification. The sections indentified as defective are **Section VI.** and **Section VII.** These sections have been amended such that they do not refer to the objections to claims 16 and 21.

If the Examiner has any questions or the Applicants can be of further assistance, the Primary Examiner is invited and encouraged to contact the Applicants' attorney at the telephone number listed below.

If there are any fees due in connection with the filing of this Amended Brief on Appeal, please charge the fees to the Deposit Account 13-0017. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and should also be charged to the Deposit Account (13-0017) indicated.

Respectfully Submitted,

April 25, 2008

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I. REAL PARTY IN INTEREST

The real party in interest of this pending patent application is Osiris Therapeutics, Inc. Osiris Therapeutics, Inc. is the owner by assignment of all rights to patent application 10/690,435. The assignment is located at reel 014959 and frame number 0831.

II. RELATED APPEALS AND INTERFERENCES

It is believed by Appellant that there are no related appeals or interferences to the instant application currently on appeal.

III. STATUS OF CLAIMS

Claims 1, 2, 4-10, and 12-28 stand rejected and currently appealed.

Claims 1, 2, 4-10, and 12-28 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

Claims 12-21 stand rejected under 35 U.S.C. § 112, first paragraph (enablement) as allegedly being anticipated non-enabling.

Claims 22-28 stand rejected, at this time, without an explanation from the Examiner and/or other Patent Office representative.[1]

[1] *See* Evidence Appendix, Advisory Action.

IV. STATUS OF AMENDMENTS

Not applicable.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention generally relates to the replacement and regeneration of cardiac tissue and muscle.[2] Mesenchymal stem cells may be used to regenerate or repair striated cardiac muscle that has been damaged through disease or degeneration.[3] Applicants have also discovered that mesenchymal stem cells may stimulate and/or promote the formation of new blood vessels in the heart and/or repair or regenerate existing blood vessels.[4]

One aspect of the present invention provides a method for producing cardiomyocytes in an individual in need thereof.[5] The method comprises the step of administering a myocardium-producing amount of mesenchymal stem cells to the individual.[6] The mesenchymal stem cells may be from a spectrum of sources, including autologous or allogeneic.[7] Mesenchymal stem cells differentiate into cardiac muscle cells and integrate with the healthy tissue of the recipient.[8] Independent Claim 1 is illustrative of the invention and reads:

> 1. A method for producing cardiomyocytes in a heart of an individual, comprising:
>
> > administering intravenously to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells in at least 20 μl and up to about 150 μl of a suspension containing 10-14 x 10^6 mesenchymal stem cells/ml, wherein said administered

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[2] Specification, page 1, lines 24-25.

[3] Specification, page 2, lines 19-21.

[4] Specification, page 9, line 33 to page 10, line 2.

[5] Specification, page 2, lines 21-23 and page 3, lines 10-13.

[6] Specification, page 3, lines 10-13.

[7] Specification, page 3, lines 22-24.

[8] Specification, page 2, lines 21-23.

> mesenchymal stem cells differentiate into cardiomyocytes.

Another aspect of the present invention is to improve ventricular function.[9] Following differentiation into cardiomyocytes, mesenchymal stem cells augment ventricular function by, for example, improving ventricular wall motion.[10] Independent Claims 4 and 22 are illustrative of this aspect of the invention. Claim 4 reads:

> 4. A method of improving ventricular wall motion of the heart of an individual, comprising:
>
> administering to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells, wherein said administered mesenchymal stem cells differentiate into cardiomyocytes, thereby improving ventricular wall motion of the heart of said individual.

Claim 22 reads:

> 22. A method of improving ventricular wall motion of the heart of an individual, comprising:
>
> administering to said individual autologous or allogeneic mesenchymal stem cells, wherein said mesenchymal stem cells are administered into an amount effective to improve ventricular wall motion of the heart of said individual.

Another aspect of the present invention provides a method of repairing or regenerating blood vessels of the heart of an individual by administering mesenchymal stem cells to the individual in an amount effective to repair or regenerate blood vessels of the heart.[11] The mesenchymal stem cells may be allogeneic or autologous.[12] The

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[9] Specification, page 7, lines 22-23.

[10] Specification, page 18, lines 23-25; Example 4, pages 15-17; and Example 5, pages 17-18.

[11] Specification, page 10, lines 2-7.

mesenchymal stem cells provide for the repair or regeneration of existing blood vessels of the heart.[13] Blood vessels which may be repaired or regenerated include arteries (including arterioles), veins, and capillaries.[14] Independent Claim 12 is illustrative of this aspect of the invention and reads:

> 12. A method of repairing or regenerating blood vessels of the heart of an individual, comprising:
>
> > administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to repair or regenerate blood vessels in the heart of said individual, wherein said administered mesenchymal stem cells differentiate into blood vessels in the heart of said individual, thereby repairing or regenerating blood vessels of the heart of said individual.

Another aspect of the present invention provides a method of stimulating or promoting the formation of new blood vessels in the heart (i.e., angiogenesis) by administering mesenchymal stem cells to the individual in an amount effective to stimulate or promote angiogenesis.[15] The mesenchymal stem cells may be allogeneic or autologous.[16] The mesenchymal stem cells promote angiogenesis.[17] New blood vessels which may be formed include arteries (including arterioles), veins, and capillaries.[18] Independent Claim 17 is illustrative of the invention and reads:

> 17. A method of stimulating or promoting angiogenesis in the heart of an individual, comprising:

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[12] Specification, page 10, lines 11-12.

[13] Specification, page 10, lines 18-20.

[14] Specification, page 10, lines 20-22.

[15] Specification, page 10, lines 2-7.

[16] Specification, page 10, lines 11-12.

[17] Specification, page 10, lines 18-20.

[18] Specification, page 10, lines 20-22.

administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to simulate or promote angiogenesis in the heart of said individual, wherein said administered mesenchymal stem cells differentiate into blood vessels in the heart of said individual, thereby promoting angiogenesis in the heart of said individual.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The principal grounds of rejection on appeal are:

(1) Whether claims 1, 2, 4-10, and 12-21 are indefinite under 35 U.S.C. § 112, second paragraph.

(2) Whether claims 12-21 are enabled under 35 U.S.C. § 112, first paragraph (enablement).

The groundless rejection of claims 22-28 is also appealed.

VII. ARGUMENT

A. Claims 1, 2, 4-10, and 12-21 are definite under 35 U.S.C. § 112, second paragraph.

1. Claims 1, 2, 4-10, and 12-21 are definite.

The Office Action dated September 22, 2006 states that independent Claims 1, 4, 12, and 17 (as well as their respective dependent claims) are unclear because the step of administering is not limited to a particular route of administration.[19] The Final Office Action maintains this rejection and states that the issue is how the administration of mesenchymal stem cells by any route, other than direct administration to the heart, would produce cardiomyocytes or promote angiogenesis limited to the heart.[20]

As an initial matter and contrary to the assertion in the Final Office Action, the claims at issue do not recite that the production of cardiomyocytes or promotion of angiogenesis is limited to the heart. The claims recite a method for producing cardiomyocytes in a heart (Claims 1 and 2) and a method of promoting angiogenesis in the heart (Claims 17-21).

The patent law requires that a patent specification conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention. 35 U.S.C. § 112, ¶ 2; *see In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970). "The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification." *Union Pac. Res. v. Chesapeake Energy*, 236 F.3d 684, 692 (Fed. Cir. 2001). Moreover, breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971); MPEP § 2173.04.

[19] Evidence Appendix, September 22, 2006 Office Action, page 2, line 26 to page 3, line 2.

[20] Evidence Appendix, Final Office Action, page 3, lines 7-8.

It is clear that Appellants are claiming methods of producing cardiomyoctyes in a heart, improving ventricular wall motion of the heart, and stimulating or promoting angiogenesis in the heart by administering autologous or allogeneic mesenchymal stem cells. More particularly and as the previous Office Actions of record have noted[21], the claims clearly encompass multiple routes of administration. Appellants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims.

Whether the claim explains the mechanism by which a particular route of administration is effective is not pertinent to a definiteness inquiry. Nevertheless, the specification clearly contemplates that mesenchymal stem cells may be administered by a variety of procedures, including localized (e.g., direct administration to the heart) or systemic administration (e.g., intravenous administration).[22] With respect to the production of cardiomyocytes in a heart, the improvement of ventricular wall motion of the heart, the repair or regeneration of blood vessels of the heart, and the promotion of angiogenesis in a heart, a reference ("Lee") cited by the September 22, 2006 Office Action[23], states that "[t]ranslplanted stem cells also undergo a 'homing' process in which they are attracted to the site of injury."[24] Thus, those skilled in the art, when reading the claims in light of the specification, would readily understand that, if administered to an individual via a variety of routes of administration (i.e., systemic or localized), the mesenchymal stem cells would travel to the heart, or be delivered to the heart site of injury, in order to produce cardiomyocytes, improve ventricular wall motion, repair or regenerate blood vessels, and/or stimulate or promote angiogenesis. Systemic or localized

[21] Evidence Appendix, September 22, 2006 Office Action, page 2, line 29 to page 3, line 2.

[22] Specification, page 3, lines 21-22; page 3, lines 27-30; page 8, lines 22-33; page 9, lines 27-31; page 10, lines 13-17.

[23] Evidence Appendix, September 22, 2006 Office Action, page 4, lines 26-28.

[24] Evidence Appendix, Lee et al., page 729, col. 2, lines 26-28.

routes of administration for biological materials are utilized within the cardiac field currently. As a result, claims 1, 2, 4-10 and 12-21 are definite.

2. Separate Argument of Patentability of Claims 5-9, 13-15, and 18-20.

The Final Office Action states that "the claims should recite: 'administering to the heart of an individual.'"[25] Appellant respectfully points out that Claims 5, 13, and 18 (and their respective dependent claims) limit the route of administration to direct administration to the heart. Claim 5 recites that the "mesenchymal stem cells are administered directly to at least one damaged portion of heart tissue." Claims 6-9 are dependent, directly or indirectly, upon Claim 5, and, therefore, include this limitation. Claims 13 and 18 recite that the "mesenchymal stem cells are administered directly to the heart." Claims 14 and 15 are dependent, directly or indirectly, upon Claim 13, and, therefore include this limitation. Likewise, Claims 19 and 20 are dependent, directly or indirectly, upon Claim 18, and, therefore include this limitation. Thus, the rejection of Claims 5-9, 13-15, and 18-20 under 35 U.S.C. § 112, second paragraph is improper in view of the explicit language of the claims. Appellants respectfully request that this rejection be reversed. Inclusion of the term "individual" is not required and irrelevant, for the instant claims on appeal and those same claims (5-9, 13-15, and 18-20) are patentable under 35 U.S.C. § 112, second paragraph.

[25] Evidence Appendix, Final Office Action, page 3, lines 19-20.

B. Claims 12-21 are enabled under 35 U.S.C. § 112, first paragraph (enablement).

The Final Office Action and the subsequent Advisory Action allege that the specification does not provide an enabling disclosure for a method of repairing or regenerating blood vessels or a method of stimulating or promoting angiogenesis.[26] Moreover, those same Actions also allege that the specification has not enabled the administration of mesenchymal stem cells to an individual by <u>any route</u>.[27]

Appellants respectfully disagree and submit that: (1) the Patent Office failed to meet its burden to establish a prima facie case that the instant claims are not enabled; and (2) the instant specification enables a person of ordinary skill in the art to practice the claimed methods.

1. The Patent Office has not met its burden.

To make a rejection for lack of enablement, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); MPEP § 2164.04. A specification that contains a teaching of the manner and process of using an invention in terms which correspond to the scope of the claims must be taken as being in compliance with the enablement requirement, unless there is reason to doubt the objective truth of the statements contained therein. MPEP § 2164.04. Thus, the burden is on the Patent Office to explain why it doubts the truth or accuracy of any statement in the supporting specification and to back up assertions with acceptable evidence or reasoning.

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[26] Evidence Appendix, Final Office Action, page 4, lines 27-30; Evidence Appendix, Advisory Action, page 3, lines 14-18.

[27] Evidence Appendix, Final Office Action, page 4, lines 27-30; Evidence Appendix, Advisory Action, page 3, lines 14-18.

See *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); MPEP § 2164.04.

a. Repairing or regenerating blood vessels and stimulating or promoting angiogenesis

Regarding methods of repairing or regenerating blood vessels and methods of stimulating or promoting angiogenesis, the Final Office Action states:

> [T]he specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the heart.[28]

However, an applicant need not have actually reduced the invention to practice prior to filing. *See Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987); MPEP § 2164.02. Moreover, lack of evidence that the claimed invention works as described will not by itself render the invention non-enabled. MPEP § 2164.02. The previous Office and Advisory Actions provide no evidence, other than mere speculation, that administering mesenchymal stem cells to achieve the effects defined in the claims would not be successful.

An *in vivo* animal model example in the specification constitutes a working example if that example correlates with a claimed method. MPEP § 2164.02. Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vivo* animal model example. MPEP § 2164.02. Moreover, a rigorous or an invariable exact correlation is not required. *See Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985); MPEP § 2164.02.

The instant application, via the "Detailed Description of the Invention" section of the specification, includes detailed *in vivo* animal model examples to illustrate the claimed

[28] Evidence Appendix, Final Office Action, page 4, lines 7-15.

invention. For example, following experimental occlusion of the left anterior descending coronary artery, mesenchymal stem cells were administered to a pig.[29] As shown in Figures 6 and 7, blood vessels were present in a generalized region of myocardial necrosis eight and twelve weeks, respectively, after the administration of the mesenchymal stem cells.[30] Moreover, mesenchymal stem cells were intimately associated with the smooth muscle layer of the blood vessels. In this respect, the mesenchymal stem cells themselves are directly involved in the repair and regeneration of blood vessels of the heart.[31] The mesenchymal stem cells also express proteins that are indicative of angiogenesis, such as Factor VIII and VEGF.[32] The Office and Advisory Actions have failed to give a reason for the presumed conclusion of a lack of correspondence between the *in vivo* animal model examples presented in Examples 6 and 7 and the claimed methods. Appellants respectfully submit that such a correspondence is provided within the instant application, rendering claims 12-21, among others, enabled under 35 U.S.C. § 112, first paragraph.

b. Route of administration.

The Final Office Action states that the mesenchymal stem cells in Example 7 of the instant specification were administered by direct injection into the heart and concludes that the instant specification does not enable administration of mesenchymal stem cells by any other route.[33] However, the Examples recited in the instant specification are meant to be merely exemplary, and not meant to limit the scope of the invention.[34] Moreover, the Office

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[29] Specification, page 18, lines 27-31; page 19, lines 19-23.

[30] Specification, page 19, lines 6-7 and Figure 6; page 19, lines 30-32 and Figure 7.

[31] Specification, page 19, line 10 and page 20, lines 1-3.

[32] Specification, page 20, lines3-8.

[33] Evidence Appendix, Final Office Action, page 4, lines 19-21 and 27-30.

[34] Specification, page 10, lines 23-24 and page 20, lines 12-15.

and Advisory Actions do not provide any evidence, other than mere speculation, that methods of administration other than direct administration of the mesenchymal stem cells to the heart would not be effective in repairing or regenerating blood vessels and stimulating or promoting angiogenesis.

The Final Office Action suggests, without providing supporting evidence for such a suggestion, that intradermal delivery of mesenchymal stem cells is unlikely to produce cardiomyocytes in the heart.[35] Even assuming that certain routes of administration would not be effective to repair or regenerate blood vessels or stimulate or promote angiogenesis, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. MPEP § 2164.08(b). The standard is whether a skilled person could determine which embodiments would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); MPEP § 2164.08(b).

The Office Actions concede that the level of skill in the art is high.[36] Moreover, as noted herein above, those skilled in the art, when reading the claims in light of the specification, would readily understand that, if administered to an individual via a variety of routes of administration (i.e., systemic or localized), the mesenchymal stem cells would travel to the heart, or be delivered to the heart site of injury, in order to produce cardiomyocytes, improve ventricular wall motion, repair or regenerate blood vessels, and/or stimulate or promote angiogenesis. The Office and Advisory Actions provide no evidence, analysis, or reasoning to support the presumed conclusion that one skilled in the art could not determine

[35] Evidence Appendix, Final Office Action, page 3, lines 8-9.

[36] Evidence Appendix, January 12, 2006 Office Action, page 6, line 11.

which embodiments would be operative. Therefore, the Patent Office did not meet its burden in showing that routes of administration other than direct administration of the mesenchymal stem cells to the heart are not enabled.

2. The instant specification enables one of ordinary skill in the art to practice the claimed methods.

The instant specification enables every step of the methods recited in claims 12-16 and 17-21. While the specification does not include specific examples of administration of mesenchymal stem cells by routes other than directly to the heart, the broad language of the specification enables a person of ordinary skill in the art to administer autologous or allogeneic mesenchymal stem cells to an individual by various routes of administration. In that respect, how a teaching is set forth, by specific example or broad terminology, is not important. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 370 (CCPA 1971); MPEP § 2164.08. The instant specification enables a person of ordinary skill in the art to administer autologous or allogeneic mesenchymal stem cells to an individual in an amount effective to repair or regenerate blood vessels or to stimulate or promote angiogenesis in the heart by disclosing, among other things, various routes of administration. For example, the instant specification broadly states:

> When the mesenchymal stem cells are administered as a cell suspension in a pharmaceutically acceptable liquid medium for injection, they may be administered locally, i.e., directly into the damaged portion of the heart, such as by an endocardial catheter for example, or they may be administered systemically, such as by intravenous administration.[37]

The instant specification, coupled with the knowledge of one of skill in the art, further provides pharmaceutically acceptable liquid media and dosages for administration.[38] Thus,

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[37] Specification, page 3, lines 21-30.

[38] *See, e.g.*, Specification, page 10, lines 7-17.

the instant specification enables a person of skill in the art to administer autologous or allogeneic mesenchymal stem cells to an individual in an amount effective to repair or regenerate blood vessels or stimulate or promote angiogenesis. Claims 12-16 and 17-21 are enabled

C. Claims 22-28

Claims 22-28 are directed to a method of improving ventricular wall motion of the heart of an individual. The method comprises the step of administering to the individual autologous or allogeneic mesenchymal stem cells. The mesenchymal stem cells are administered in an amount effective to improve ventricular wall motion of the heart.

Claims 22-28 were submitted with Applicants' June 25, 2007 Amendment after Final Rejection[39] and entered pursuant to the Advisory Action.[40] However, the Advisory Action did not provide an explanation of how the new claims are rejected for purposes of patentability. Thus, the Patent Office has not met its burden in showing that Claims 22-28 should be rejected.

VIII. CONCLUSION

Appellants respectfully request reversal of the Examiner's rejection of claims 1, 2, 4-10, and 12-21 as being indefinite under 35 U.S.C. § 112, second paragraph.

Appellants respectfully request reversal of the Examiner's rejection of claims 12-21 as not being enabled under 35 U.S.C. § 112, first paragraph (enablement).

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[39] Evidence Appendix, Applicants' Response of June 25, 2007, pages 5-6.

[40] Evidence Appendix, Advisory Action, page 1, number 7.

Appellants respectfully request reversal of the Examiner's groundless rejection of claims 22-28.

Please charge the fees due pursuant to 37 C.F.R. §41.20(b)(2) to the Deposit Account 13-0017. If there are any other fees due in connection with the filing of this Brief on Appeal, please charge the fees to the Deposit Account 13-0017. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and should also be charged to the Deposit Account (13-0017) indicated.

Respectfully Submitted,

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IX. CLAIMS APPENDIX

Claims On Appeal

1. (Previously presented) A method for producing cardiomyocytes in a heart of an individual, comprising:

administering intravenously to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells in at least 20 μl and up to about 150 μl of a suspension containing 10-40 x 10^6 mesenchymal stem cells/ml, wherein said administered mesenchymal stem cells differentiate into cardiomyocytes.

2. (Original) The method of Claim 1 wherein said individual is administered from 40 μl to 150 μl of a suspension containing 10-40 x 10^6 mesenchymal stem cells/ml.

3. Canceled.

4. (Previously presented) A method of improving ventricular wall motion of the heart of an individual, comprising:

administering to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells, wherein said administered mesenchymal stem cells differentiate into cardiomyocytes, thereby improving ventricular wall motion of the heart of said individual.

5. (Original) The method of Claim 4 wherein said mesenchymal stem cells are administered directly to at least one damaged portion of heart tissue.

6. (Original) The method of Claim 5 wherein the mesenchymal stem cells are administered by injection.

7. (Original) The method of Claim 6 wherein the mesenchymal stem cells are administered in a pharmaceutically acceptable liquid injectable carrier.

8. (Original) The method of Claim 5 wherein the mesenchymal stem cells are administered during an open surgical procedure.

9. (Original) The method of Claim 8 wherein the mesenchymal stem cells are administered by injection.

10. (Original) The method of Claim 4 wherein the mesenchymal stem cells are administered intravenously.

11. Canceled.

12. (Previously presented) A method of repairing or regenerating blood vessels of the heart of an individual, comprising:

administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to repair or regenerate blood vessels in the heart of said individual, wherein said administered mesenchymal stem cells differentiate into blood vessels in the heart of said individual, thereby repairing or regenerating blood vessels of the heart of said individual.

13. (Original) The method of Claim 12 wherein said mesenchymal stem cells are administered directly to the heart.

14. (Original) The method of Claim 13 wherein said mesenchymal stem cells are administered by injection.

15. (Original) The method of Claim 14 wherein the mesenchymal stem cells are administered in a pharmaceutically acceptable liquid injectable carrier.

16. (Original) The method of Claim 12 wherein said mesenchymal stem cells are allogeneic to the individual.

17. (Previously presented) A method of stimulating or promoting angiogenesis in the heart of an individual, comprising:

administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to stimulate or promote angiogenesis in the heart of said individual, wherein said administered mesenchymal stem cells differentiate into blood vessels in the heart of said individual, thereby promoting angiogenesis in the heart of said individual.

18. (Original) The method of Claim 17 wherein said mesenchymal stem cells are administered directly to the heart.

19. (Original) The method of Claim 18 wherein said mesenchymal stem cells are administered by injection.

20. (Original) The method of Claim 19 wherein said mesenchymal stem cells are administered in a pharmaceutically acceptable liquid injectable carrier.

21. (Original) The method of Claim 17 wherein said mesenchymal stem cells are allogeneic to the individual.

22. (Previously Presented). A method of improving ventricular wall motion of the heart of an individual, comprising:

administering to said individual autologous or allogeneic mesenchymal stem cells, wherein said mesenchymal stem cells are administered into an amount effective to improve ventricular wall motion of the heart of said individual.

23. (Previously Presented). The method of Claim 22 wherein said mesenchymal stem cells are administered directly to at least one damaged portion of heart tissue.

24. (Previously Presented). The method of Claim 23 wherein the mesenchymal stem cells are administered by injection.

25. (Previously Presented). The method of Claim 24 wherein the mesenchymal stem cells are administered in a pharmaceutically acceptable liquid injectable carrier.

26. (Previously Presented). The method of Claim 23 wherein the mesenchymal stem cells are administered during an open surgical procedure.

27. (Previously Presented). The method of Claim 26 wherein said mesenchymal stem cells are administered by injection.

28. (Previously Presented). The method of Claim 22 wherein the mesenchymal cells are administered intravenously.

X. EVIDENCE APPENDIX

A. **Lee et al.**

B. **January 12, 2006 Office Action**

C. **September 22, 2006 Office Action**

D. **Final Office Action**

E. **Applicants' Response of June 25, 2007**

F. **Advisory Action**

Stem-Cell Transplantation in Myocardial Infarction: A Status Report

Michael S. Lee, MD, and Raj R. Makkar, MD

Myocardial infarction is the leading cause of congestive heart failure and death in the industrialized world. Current therapy is limited in preventing the progression of ventricular remodeling and congestive heart failure. Recent interest has focused on stem cells, which are undifferentiated and pluripotent cells that can proliferate, potentially self-renew, and differentiate into cardiomyocytes. Myocardial regeneration with stem-cell transplantation is a possible treatment option to reverse the deleterious hemodynamic and neurohormonal effects that occur after myocardial infarction and can lead to congestive heart failure. Various preclinical animal studies show the potential to regenerate myocardium and improve perfusion to the infarct area to improve cardiac function but also suggest that stem cells may have proarrhythmic effects. Early phase I clinical studies indicate that stem-cell transplantation is feasible and may have beneficial effects on ventricular remodeling after myocardial infarction. Future randomized clinical trials will establish the magnitude of the benefit and the effects on arrhythmias after stem-cell therapy.

Ann Intern Med. 2004;140:729-737. www.annals.org
For author affiliations, see end of text.

Myocardial infarction is the leading cause of congestive heart failure and death in developed countries. Congestive heart failure affects approximately 5 million patients in the United States, with 400 000 new cases per year (1). The current pharmacotherapy for congestive heart failure, including neurohormonal inhibition with angiotensin-converting enzyme inhibitors and β-blockers, improves clinical outcomes. Despite this, other treatment options that include various interventional and surgical therapeutic methods are limited in preventing ventricular remodeling because of their inability to repair or replace damaged myocardium. Given the high morbidity and mortality rates associated with congestive heart failure, dearth of donor hearts for transplantation, complications associated with immunosuppression, and long-term failure of transplanted organs, novel treatment methods that improve cardiac function and prevent heart failure are in demand.

Although human cardiomyocytes are reported to proliferate and contribute to the increase in muscle mass of the myocardium after myocardial infarction (2), their capacity for regeneration, mitigation of the adverse effects of ventricular remodeling, and contribution to cardiac function is limited. Neovascularization in the infarcted myocardium plays an important part in ventricular remodeling (3). After myocardial infarction, the newly formed capillary network in the infarcted myocardium cannot adequately keep up with the tissue growth needed for contractile compensation and cannot meet the higher demands of the surviving hypertrophied cardiomyocytes, leading to further expansion of the infarct and fibrosis of the myocardium (4). Thus, neovascularization represents a potentially important process by which increasing perfusion to infarcted myocardium may reduce ventricular dilatation and improve cardiac function through the rescue of hibernating myocardium and decreased apoptosis of hypertrophied cardiomyocytes. Congestive heart failure after an extensive myocardial infarction may occur when compensatory mechanisms are overwhelmed.

In this article, we critically review the existing literature on stem-cell transplantation. Most data come from animal models and phase I clinical studies that are small, uncontrolled, and very preliminary.

Cellular Cardiomyoplasty Approaches

The adult heart appears to contain a subpopulation of cardiomyocytes that are not terminally differentiated and re-enter the cell cycle and undergo nuclear mitotic division soon after myocardial infarction (2). Despite this, myocardium does not substantially regenerate after myocardial infarction. Cellular cardiomyoplasty, which is the replacement or regeneration of cardiomyocytes through cell transplantation, may be attained in one of the following ways: 1) by transplanting stem cells that differentiate into cardiomyocytes or promote angiogenesis; 2) by mobilizing bone marrow resident stem cells to the site of injury with the use of cytokines, such as granulocyte colony-stimulating factor and stem-cell factor (5); or 3) by administering local treatment with growth factors, such as insulin-like and hepatocyte growth factors, that induce the differentiation of cardiac progenitor cells into cardiomyocytes (6).

Stem cells, or immature tissue precursor cells, are undifferentiated cells that can proliferate, potentially self-renew, and differentiate into 1 or more types of specialized cells, including cardiomyocytes (7). The genetic and cellular mechanisms that initiate transdifferentiation of stem cells are poorly understood. Transplanted stem cells also undergo a "homing" process in which they are attracted to the site of injury (8). The exact homing mechanism and organ-specific differentiation signals for stem cells are not clearly understood but may be related to microenvironmental factors that are favorable to stem-cell growth and function, integrin and other adhesion molecules, homing receptors, ischemia, and increased expression of vascular endothelial growth factor (9, 10).

Another strategy for cellular cardiomyoplasty involves an indirect approach. Bone marrow stem cells, which were mobilized by systemic injections of cytokines (such as granulocyte colony-stimulating factor and stem-cell factor)

Table 1. List of Donor Cells

Donor Cell	Advantages	Disadvantages
Fetal cardiomyocytes	Cardiomyocyte phenotype	Immunosuppression required, ethical debate, short survival, and limited supply
Skeletal myoblasts	Lack of immunogenicity; autologous transplantation; high yield; and fatigue-resistant, slow-twitch fibers	Arrhythmogenic and lack of gap junction
Endothelial progenitor cells	Lack of immunogenicity and autologous transplantation	Need for expansion because of limited supply
Embryonic stem cells	Pluripotent and highly expandable	Immunosuppression required, ethical debate, lack of availability, and tumor potential
Adult mesenchymal stem cells	Lack of immunogenicity, autologous transplantation, pluripotent, and cryopreservable for future use	Unclear functional and electrophysiologic properties and difficult to isolate and propogate in culture

homed to the infarcted myocardium, replicated, differentiated, promoted myocardial repair, and improved cardiac function in a murine model (5).

A less common strategy for cellular cardiomyoplasty is the use of growth factors, such as insulin-like and hepatocyte growth factors, to attract cardiac progenitor cells, induce the differentiation of cardiac progenitor cells into cardiomyocytes, and promote cardiomyocyte replication (6). Insulin-like growth factor also protects against cardiomyocyte death and attenuates left ventricular remodeling in a mouse model.

To be clinically useful, stem-cell proliferation must be rapid and sustained and provide for effective physical and electrical coupling of the new cells (11). These processes must occur while the myocardium maintains its usual function of pumping blood and perfusing tissues. Meanwhile, all these processes depend on the simultaneous formation of nutritive vascular structures.

DONOR CELLS

The ideal donor cell is the subject of intense scientific, ethical, and political debate. Different donor cells might replace necrotic myocardium and minimize remodeling. We discuss the strategic rationale for each cell type and its advantages and disadvantages (**Table 1**).

Fetal Cardiomyocytes

Soonpaa and colleagues (12) demonstrated that transplanted fetal cardiomyocytes could survive, proliferate, and form nascent intercalated disks with host myocardium in murine models. Transplanting fetal cardiomyocytes into a myocardial scar formed new cardiac tissue and improved cardiac function (13, 14). In another study, Etzion and colleagues (15) reported attenuation of ventricular dilatation, infarct thinning, and cardiac dysfunction after embryonic cardiomyocytes were transplanted into rat hearts after myocardial infarction. Fetal cardiomyocytes may also contribute to the release of cardioprotective factors, such as vascular endothelial growth factor, through a paracrine effect that stimulates nascent blood vessel formation in grafted areas and host ventricle (16). Increased microcirculation provides the transplanted cells not only with increased perfusion but may also be a means to remove necrotic debris from myocardial infarction. However, allogeneic cell transplantation with human fetal cardiomyocytes is limited because of the unresolved ethical debates and the inability to obtain enough cells to repair damaged myocardium.

Skeletal Myoblasts

Skeletal myoblasts function as precursor cells that can undergo mitosis, proliferate, form syncytium, and ultimately form new skeletal myocytes (17). Autologous skeletal myoblasts are ideal for transplantation because they are readily available with a skeletal muscle biopsy specimen from the patient, can be returned after in vitro expansion, and do not carry immunologic and ethical concerns as human embryonic stem cells do. Skeletal myoblasts strongly resist ischemia, allowing for increased survival and engraftment in areas of poor coronary perfusion, which is often seen in patients with coronary artery disease (18).

Jain and colleagues (19) showed that implantation of skeletal myoblasts formed viable myoblast implants and attenuated ventricular dilatation, thereby improving exercise capacity, cardiac function, and left ventricular systolic pressures after myocardial infarction in a rat model. Similarly, transplanting autologous skeletal myoblasts in an infarcted area minimized left ventricular dysfunction and improved systolic function in the scarred myocardium through colonization of fibrosis by skeletal muscle cells with the expression of myosin heavy chain after myocardial infarction in a sheep model for up to 1 year (20). The degree of improvement of cardiac function is related to the number of myoblasts injected (21). The potential for intravascular delivery of skeletal myoblasts also makes these cells particularly appealing as the donor cell of choice (22).

Endothelial Progenitor Cells

Neovascularization is paramount to the survival of the newly formed cardiomyocytes. Endothelial progenitor cells are bone marrow residents that can be released into circulation after an acute myocardial infarction and can produce neovascularization in the adult (23–25). Endothelial progenitor cells are ideal donor cells because they allow autologous harvesting, obviating the need for immunosuppression. The intravenous administration of ex vivo expanded endothelial progenitor cells enhanced neovascularization, reduced left ventricular dilatation, and preserved cardiac function after myocardial infarction in a rat model (26). Similarly, Kocher and colleagues (27) intravenously administered granulocyte colony-stimulating factor–mobilized, human bone marrow–derived endothelial progenitor cells that migrated into the infarcted region within 48 hours, transdifferentiated into endothelial cells, induced neovascularization, limited apoptosis of the hypertrophied

cardiomyocytes in the peri-infarct area and ventricular remodeling, and improved cardiac function after myocardial infarction in a rat model. Endothelial progenitor cells might also transdifferentiate into cardiomyocytes and thus participate in myocardial regeneration (28, 29).

A major obstacle to the clinical application of stem cells is the limited number of cells that can be harvested from the patient. Methods to potentially expand populations of endothelial progenitor cells ex vivo have been developed (26). However, expanding endothelial cells may suppress their homing capacity and limit their effectiveness (30). Treatment with statins in patients with coronary artery disease increased the proportion of endothelial progenitor cells in circulation (31). Autologous bone marrow cells secrete angiogenic factors, such as vascular endothelial growth factor and macrophage chemoattractant protein-1, that stimulate the proliferation of endothelial cells and increase collateral perfusion and cardiac function after catheter-based transendocardial injection into ischemic myocardium (32).

Embryonic Stem Cells

Human embryonic stem cells are pluripotent cells that can differentiate into all cell types of the body, including cardiomyocytes, but with a much lower efficiency of conversion into cardiomyocytes compared with those of mice (33, 34). In a rat model, intramyocardial injection of embryonic stem cells engrafted in the myocardium and improved cardiac function and myocardial contractility after myocardial infarction (35).

The main drawback with transplanting animal embryonic stem cells into human hearts includes immune rejection due to tissue incompatibility at the HLA level (11). The requirement for immunosuppression to prevent destruction of the cellular transplant will probably detract investigators from pursuing clinical trials with animal embryonic stem cells.

Transplantation of human embryonic stem cells is advantageous because of the minimal immunoreactivity, which is due to the reduced expression of immune-related cell-surface proteins (36). However, the future application of human embryonic stem cells in clinical trials is limited because of their lack of availability and intense ethical and political issues that are unresolved (37). Currently, President George W. Bush has limited funding of research in human embryonic stem cells to those already established.

Adult Mesenchymal Stem Cells

Human adult mesenchymal stem cells are accessible from the bone marrow and peripheral blood, allow autologous transplantation, and are pluripotent cells, which can differentiate into specialized tissues, including cardiomyocytes, endothelial cells, and smooth-muscle cells (38–41). Mesenchymal stem-cell transplantation obviates the need for immunosuppression even when allogenic stem cells are used. Implanting autologous or allogenic swine mesenchymal stem cells after myocardial infarction sustained engraftment in host myocardium, differentiated into cardiomyocytes, maintained wall thickness, reduced ventricular remodeling, and improved cardiac function (42–44). In another study, Min and colleagues (45) reported improvement in cardiac function and resting blood flow in infarcted myocardium with intramyocardial transplantation of human mesenchymal stem cells and a statistically significantly greater improvement in cardiac function and resting blood flow with cotransplantation of human fetal cardiomyocytes after myocardial infarction in a porcine model.

Mesenchymal stem cells injected with fresh bone marrow into infarcted myocardium induced the overexpression of cardiac tenascin and sympathetic nerve sprouting, resulting in myocardial sympathetic hyperinnervation in swine (46). The tenascin gene family of extracellular matrix proteins is implicated in nerve regeneration (47–49), cardiac remodeling (50), vascular remodeling (51–53), and neointimal proliferation (54). This mechanism may explain improved myocardial function after mesenchymal cell transplantation. However, sympathetic hyperinnervation may lead to life-threatening ventricular tachyarrhythmias (55, 56).

Treatment with 5-azacytidine (a DNA-demethylating agent) of adult mesenchymal stem cells from abdominal subcutaneous fatty tissue induced direct differentiation into cardiomyocytes in a rabbit model (57). Similarly, Tomita and colleagues (58) reported that bone marrow cells cultured with 5-azacytidine differentiated into cardiac-like cells before injection and in vivo in myocardial infarction and improved cardiac function. Pretreating autologous mesenchymal stem cells with 5-azacytidine before transplantation into infarcted myocardium may increase the likelihood of successful regeneration of infarcted myocardium.

ROUTE OF DELIVERY

Intramyocardial Injection

Orlic and colleagues (59) isolated bone marrow stem cells and directly injected them in the margin bordering the infarct of the left ventricle of mice. These cells migrated into the region bordering the infarction and differentiated into cardiomyocytes and endothelial cells, generating de novo myocardium, improving cardiac function, and leading to neovascularization. Direct intramyocardial injection may require fewer cells to achieve engraftment compared with intracoronary or intravenous administration. Although the injection process is simple and can be performed by direct inspection of the potential target zones (37), this invasive delivery in the form of cardiac surgery is associated with intraoperative and postoperative risks and had a success rate of 40% in 1 study in a mouse model (59).

A different approach is to implant stem cells through percutaneous catheter-based myocardial injections guided by electromechanical mapping (60). Electromechanical mapping can delineate and identify scarred and viable

Table 2. **Phase I Clinical Studies of Stem-Cell Transplantation**

Study, Year (Reference)	Study Sample, *n*	Mode of Delivery	Associated Procedure	Follow-up	Donor Cell	Results	Complications
Hamano et al., 2001 (66)	5	Myocardial injection	CABG	1 y	Bone marrow cells	Increased myocardial perfusion	None
Strauer et al., 2002 (63)	10	Intracoronary infusion	PTCA	3 mo	Bone marrow cells	Increased myocardial perfusion and improved contractile function	None
Assmus et al., 2002 (64)	20	Intracoronary infusion	PTCA	4 mo	Progenitor cells	Increased myocardial perfusion and improved contractile function	None
Menasché et al., 2003 (67)	10	Myocardial injection	CABG	10.9 mo	Skeletal myoblasts	Improved contractile function and improvement in heart failure symptoms	1 death (68) and 4 patients with ventricular tachycardia
Stamm et al., 2003 (69)	6	Myocardial injection	CABG	3–9 mo	Bone marrow cells	Increased myocardial perfusion	2 patients with supraventricular tachycardia
Pagani et al., 2003 (70)	5	Myocardial injection	LVAD	68–191 d	Skeletal myoblasts	Development of myotubes	4 patients with arrhythmias and 1 LVAD death
Tse et al., 2003 (60)	8	Myocardial injection	Catheterization	3 mo	Bone marrow cells	Improvement in anginal symptoms, myocardial perfusion, and contractile function	None
Perin et al., 2003 (71)	14	Myocardial injection	Catheterization	4 mo	Bone marrow cells	Improved myocardial perfusion and contractile function	1 death
Wollert et al., 2003 (72)	30	Intracoronary infusion	PTCA	6 mo	Bone marrow cells	Improved contractile function	None

* CABG = coronary artery bypass grafting; LVAD = left ventricular assist device; PTCA = percutaneous transluminal coronary angioplasty.

myocardium and allow assessment of the transmural extent of myocardial infarction so that each injection can be precisely targeted to viable areas of hibernating myocardium (61, 62).

Intracoronary Injection

A percutaneous transluminal coronary catheter can be used for intracoronary administration of bone marrow–derived stem cells after myocardial infarction (63). This is advantageous over intravenous administration because it can deliver the maximum concentration of cells to the site of infarct and peri-infarct tissue during the first passage. Intracoronary administration into the infarct artery allows the stem cells to home in and incorporate into the areas bordering the infarct zone in a homogenous manner. This is in contrast to direct myocardial injection, which may lead to "islands" of cells in the infarcted myocardium, providing a substrate for electrical instability and ventricular tachyarrhythmias (64). High-pressure injection of stem cells into the infarct region may facilitate transendothelial passage and migration into infarcted myocardium (63). Because coronary flow impairment and myocardial cell necrosis are possible, the quantity of cells and duration of infusion must be carefully determined (37).

Intravenous Injection

Intravenous administration of stem cells is an attractive and practical mode of delivery because it does not require cardiac surgery or catheterization (27). If stem cells have an effective cellular homing mechanism to localize in the infarcted myocardium, intravenous administration of stem cells may be possible. Microenvironmental factors, expression of matrix and adhesion molecules by injured tissue, homing receptors, and various factors relating to migration are believed to be involved in the homing process of stem cells (65). However, homing of stem cells to other organs could limit the percentage of cells reaching the infarct region after intravenous administration.

Phase I Clinical Studies

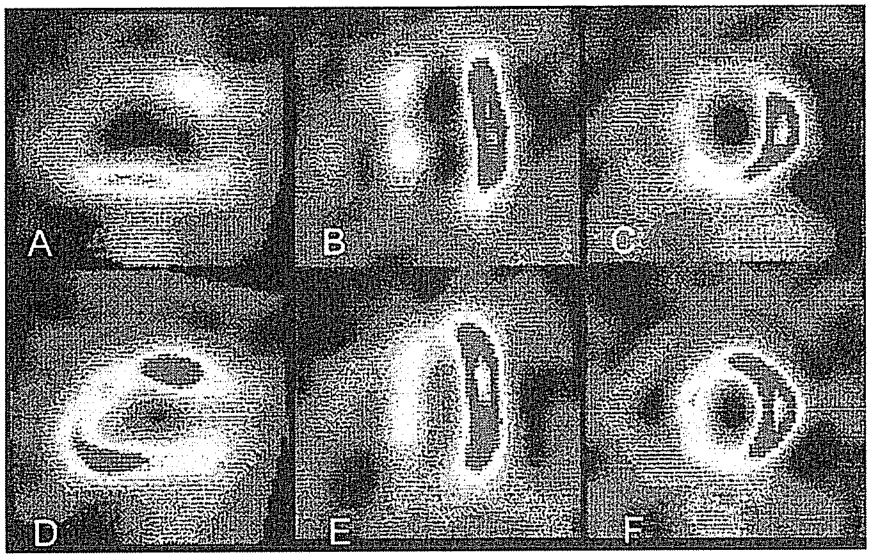
Thus far, human studies on stem-cell transplantation have been small and nonrandomized. We discuss the clinical studies that have been conducted with stem-cell transplantation.

Hamano and colleagues (66) locally injected autologous bone marrow cells into areas of ischemic myocardium during coronary artery bypass grafting in 5 patients (**Table 2**). Perfusion increased in the treated area of the myocardium in 3 patients. Coronary angiography also demonstrated the formation of new collateral blood vessels at this site.

Strauer and colleagues (63) transplanted autologous mononuclear bone marrow cells into the infarct-related artery during percutaneous transluminal coronary angioplasty in patients 6 days after acute myocardial infarction. The 10 patients treated with stem cells had smaller infarct areas and improved stroke volume index, left ventricular end-systolic volume, contractility of the infarct area, and myocardial perfusion of the infarct region compared with 10 patients in the control group (**Figure 1**).

The Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) (64) study included 20 patients who underwent primary angioplasty and stenting and were given intracoronary infusion of autologous progenitor cells. The transplantation of both circulating blood–derived and bone marrow–derived progenitor cells had beneficial effects on postinfarction left ventricular remodeling process, regional contractile function of the infarct zone, and coronary blood flow reserve in the infarct-related artery.

Figure 1. **Improved myocardial perfusion of infarcted anterior wall detected by 201-thallium scintigraphy 3 months after intracoronary transplantation of autologous, mononuclear bone marrow cells subsequent to an acute anterior myocardial infarction.**



The images on the left (*A, D,* sagittal) and in the middle (*B, E*) show the long axis, whereas the images on the right (*C, F,* frontal) show the short axis of the heart. Initially, the anterior wall, with green apical and anterior regions, had reduced myocardial perfusion (*A, B, C*). Three months after cell transplantation, the same anterior wall (yellow) revealed a significant improvement in myocardial perfusion (*D, E, F*). All images were obtained during the exercise phase. Reproduced with permission from Strauer BE, Brehm M, Zeus T, Kostering M, Hernandez A, Sorg RV, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation. 2002;106:1913-8 (63).

Menasché and colleagues (67) reported improvement in local myocardial contractility and viability in the grafted scar on echocardiography and positron emission tomography after autologous skeletal myoblasts were injected into the postinfarction scars of 10 patients during coronary artery bypass grafting. One patient died of a stroke 17.5 months after cell transplantation (68). Four patients developed sustained ventricular tachycardia and were implanted with an internal defibrillator. New York Heart Association functional class also improved.

Stamm and colleagues (69) locally implanted autologous bone marrow stem cells in the infarcted region during coronary artery bypass grafting in 6 patients. Although local contractility did not increase, myocardial perfusion on single-photon emission computed tomography strikingly improved in 5 patients. Two patients experienced supraventricular tachycardia.

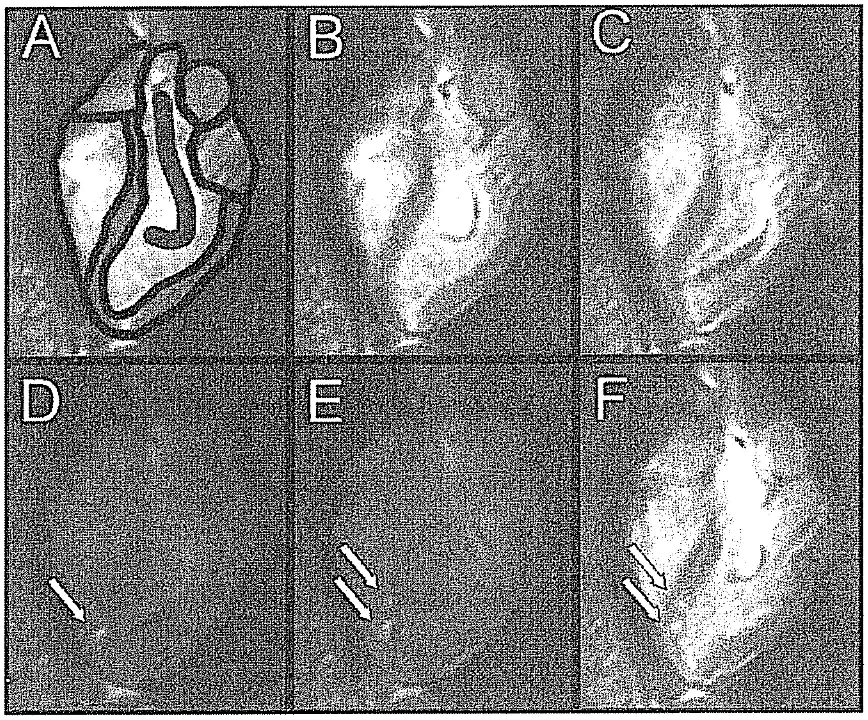
At the time of implantation of left ventricular assist device, Pagani and colleagues (70) injected autologous skeletal myoblasts into the zone of scarred myocardium of 5 patients with ischemic cardiomyopathy who were on a waiting list for cardiac transplantation. Upon explantation of the heart, the implanted skeletal myoblasts showed evidence of viability in the scarred myocardium and differentiated into mature myofibers. Four patients experienced cardiac arrhythmias. Two patients experienced postoperative atrial fibrillation, and 3 patients experienced ventricular tachyarrhythmias.

Tse and colleagues (60) implanted autologous bone marrow mononuclear cells through percutaneous catheter-based myocardial injections guided by electromechanical mapping in 8 patients with stable angina refractory to maximal medical therapy. Patients had less angina and improved myocardial perfusion and segmental contractility at the ischemic region on cardiac magnetic resonance imaging (MRI).

Perin and colleagues (71) also implanted autologous bone marrow mononuclear cells into hibernating myocardium through percutaneous catheter-based myocardial injections guided by electromechanical mapping in 14 patients with severe chronic ischemic heart failure. Single-photon emission computed tomography myocardial perfusion scintigraphy revealed a statistically significant reduction in the reversible stress defects and improvement in global left ventricular systolic function in treated patients. One patient died at 14 weeks, presumably of sudden cardiac death.

The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) (72) study was one of the first randomized, controlled studies of stem-cell transplantation in patients with acute myocardial infarction. Cardiac MRI showed improved left ventricular function in 30 patients treated with intracoronary transfer of autologous bone marrow cells to the infarct-related coronary arteries after successful percutaneous coronary intervention.

Figure 2. **Representative sequence of 2 septal endomyocardial injections.**



A. Overlay to identify the 4 cardiac chambers and pulmonary artery, as well as the intracardiac-guiding catheter-receiver coil. B. Intracardiac-guiding catheter-receiver coil directed toward the interventricular septum without making direct contact. C. The spring-loaded 27-gauge injection needle (Stiletto; Boston Scientific, Maple Grove, Minnesota) is extended from the guiding catheter and engages the apical septum of the left ventricle. D. The same view with saturation preparation for background suppression. The first injection of gadolinium appears bright (*arrow*). E. The second injection is made 1 minute later, more proximally along the septum, with the same imaging plane as before. Gadolinium from the first, more distal, injection site remains visible. F. After saturation pulses are stopped, both injections remain visible in the myocardium. Injections typically remained visible for more than 10 minutes. Reproduced with permission from Lederman RJ, Guttman MA, Peters DC, Thompson RB, Sorger JM, Dick AJ, et al. Catheter-based endomyocardial injection with real-time magnetic resonance imaging. Circulation. 2002;105:1282-4 (75).

IMAGING TECHNIQUES

The fate of transplanted stem cells in animal models has been mainly assessed postmortem by histologic analysis. Noninvasive in vivo imaging techniques are needed in upcoming clinical trials to monitor and detail donor cell delivery, myocardial differentiation, integration into the damaged myocardium, and contribution to cardiac function. Delivery of mesenchymal stem cells with radiograph fluoroscopy is limited because of the inability to verify whether the injection was successful. Cardiac MRI successfully detected and tracked intramyocardial injection of magnetically labeled mesenchymal stem cells after myocardial infarction in a swine model (73). Similar results were obtained with targeted catheter-based implantation of iron-loaded myogenic precursor cells into infarcted myocardium in a swine model (74). Cardiac MRI allows the accurate noninvasive in vivo assessment of the size and location of the intramyocardial injection, thus providing information on the extent of stem-cell retention. Magnetic resonance imaging can also be used to guide catheter-based cardiac injections (**Figure 2**) (75). Percutaneous endomyocardial drug delivery was conducted with real-time MRI and allowed for precise 3-dimensional localization of injections in the left ventricular wall in swine.

Human endothelial progenitor cells were radioactively labeled with 111-indium oxine, a safe and commercially available radioactive tracer for monitoring blood cells for inflammation scintigraphy, and were administered by intravenous and left ventricular intracavitary route for the in vivo monitoring of their fate after myocardial infarction in a rat model (76, 77). Scintigraphic images obtained after injection of 111-indium oxine–labeled endothelial progenitor cells demonstrated increased homing of transplanted cells and tracer uptake in the heart after myocardial infarction. This suggests that radiolabeling with 111-indium oxine is a potential technique to noninvasively monitor transplanted endothelial progenitor cells and assess the fate and tissue distribution of these cells in the myocardium after myocardial infarction in clinical practice.

UNRESOLVED ISSUES

Many important fundamental questions about stem-cell transplantation still remain unanswered. The optimal

donor cell and the optimal number of stem cells to be transplanted have not been determined. There is a threshold of the number of stem cells needed to generate adequate heart muscle to contribute to cardiac function. Adult stem cells are limited in supply in each patient and therefore are difficult to isolate and purify. The stem cells from the patient's body must be isolated and expanded in culture to obtain a sufficient amount for stem-cell transplantation. Manipulation in vitro of stem cells by providing optimal culture condition, which include various cytokines and growth factors to augment organ-specific engraftment, may be needed to facilitate in vivo incorporation (78).

Whether the most benefit from transplantation is derived early after acute myocardial infarction during extreme local inflammation, later during the ventricular remodeling phase, or late at the end stage of ischemic cardiomyopathy is uncertain. The inflammatory process is strongest in the first days after acute myocardial infarction and may be responsible for the negative results after immediate cell transplantation (79). Transplantation after 2 weeks after infarct scar formation may reduce the benefits of cell transplantation. Therefore, transplanting stem cells between 7 and 14 days after acute myocardial infarction seems reasonable.

The ideal strategy of delivery (intramyocardial injection, intracoronary administration, or systemic delivery) has not been clarified. The long-term viability and function of stem cells are also uncertain. The strategy of co-administering stem cells with angioblasts may have synergistic effects by augmenting perfusion to both the chronically ischemic native myocardium and the newly administered stem cells.

Data on stem-cell transplantation in myocardial infarction are limited because the large proportion of the work has been done in laboratories and animal models. While these results are interesting and perhaps safe and promising, the data are very preliminary, with the phase I clinical studies being conducted in an uncontrolled manner with few patients. Whether stem-cell transplantation will fulfill the potential in replacing damaged myocardium in patients and prevent congestive heart failure, and therefore apply to the large population of postinfarction patients, must be evaluated by rigorous large-scale clinical trials.

SAFETY

Safety is always a major concern in dealing with clinical trials involving stem cells. Implanted stem cells may differentiate into fibroblasts rather than myocytes. This may enhance scar formation, further depressing myocardial function and creating a substrate for life-threatening arrhythmias (80). There may also be life-threatening consequences if stem cells incompletely integrate into the myocardium and adversely affect electrical conduction and syncytial contraction of the heart (11). Tumor formation associated with embryonic stem cells, such as teratomas, may also occur.

Late-onset toxicity may occur from using whole populations of bone marrow mononuclear cells, which contain different organ-specific stem cells (77). These nonessential cells may incorporate into regenerating myocardium, resulting in the generation of noncardiac tissues.

SUMMARY

Stem-cell transplantation in acute myocardial infarction is still in its infancy. The potential for stem cells to acutely regenerate contracting myocardium and improve immediate and long-term prognosis after acute myocardial infarction faces some formidable challenges. Whether stem-cell transplantation offers a sustained clinical benefit by reversing ventricular remodeling in myocardial infarction is unknown, given that too few patients have undergone stem-cell transplantation to derive any meaningful efficacy and safety data. Preliminary data from animal models suggest that infarcted myocardium can be regenerated by implanting stem cells. Skepticism exists with this treatment method, especially given the initial excitement of angiogenesis studies that did not live up to expectations and the disappointment in gene therapy trials. More work needs to be done to clarify the biology of stem cells and address any unanswered questions for clinical use. Currently, the effectiveness of stem-cell transplantation alone is difficult to interpret because the clinical studies have been done in conjunction with percutaneous or surgical revascularization. Thus, larger double-blinded, controlled studies with therapeutic end points are imperative to clarify the role of stem-cell transplantation for myocardial regeneration.

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Potential Financial Conflicts of Interest: None disclosed.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,435	10/21/2003	Mark F. Pittenger	640100.470	3718

7590 01/12/2006

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/690,435	PITTENGER ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 12 December 2005.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) 12-21 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11/12/2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed December 12, 2005. Applicant's response to restriction requirement of November 3, 2005 has been entered. No claims were amended or withdrawn. Currently, claims 1-21 are pending in the application.

Election/Restrictions

Applicant's election of Group I (claim 1-11), with traverse, drawn to a method producing cardiomyocytes and for improving ventricular wall motion in a heart of an individual, comprising administration of cardiomyocyte producing mesenchymal stem cells (MSCs), is acknowledged. Claims 12-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the Paper filed December 12, 2005. Because Applicant did not distinctly and specifically point out the supposed errors in the examiner's action, the requirement for restriction is maintained and hereby made FINAL.

Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 1-2 and 4-10 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method producing cardiomyocytes in a heart of an individual, comprising: administering to said individual a cardiomyocyte producing amount of autologous or allogeneic MSCs, does not reasonably provide an enablement for a method of administering said MSCs from any source, including xenogeneic, or MSCs that are genetically modified, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

Claim 1 is drawn to a method producing cardiomyocytes in a heart of an individual, comprising: administering intravenously to said individual a cardiomyocyte producing amount of MSCs. Claims 2 further limits the dose of MSCs administered. Claim 4 is drawn to a method of improving wall motion of the heart of an individual, comprising administering to said individual a cardiomyocyte producing amount of MSCs. Claims 5-10 further limit claim 4 to routes of administration and administration during open surgical procedure. When given their broadest reasonable interpretation, in view of the as filed specification, claims 1-2 and 4-10 encompass methods of administering said MSCs from any source, including cells that are xenogeneic in origin. The specification teaches that the MSCs may be genetically modified or engineered to contain genes which express proteins of importance for differentiation and/or maintenance of striated muscle cells (line 15-17, p. 4). The specification additionally envisions the use of MSCs "in accordance with the invention, in order of preference, autologous, allogeneic or xenogeneic (lines 15-16, p. 8).

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to MSCs from any source, including xenogeneic, or MSCs that are genetically modified, to produce cardiomyocytes in a heart of an individual or improve ventricular wall motion, as claimed in claims 1-2, and 4-10 of the instant application.

The Unpredictability Of The Art And The State Of The Prior Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art with regard to transplantation of MSCs and gene therapy are effectively summarized by the references of Prockop (Science 276:71-74, 1997; of record); Gerson, S. (Nature Medicine 5:262-264, 1999; of record); Saadi et al. (Life Sciences 62:365-387, 1998); and Verma et al. (Nature 389:239-242, 1997, of record).

The prior art at the time of filing suggests that MSC transplantation and *in vivo* therapeutic effectiveness have not been established such that utilizing these cells to treat diseases, disorders, or conditions is routine or predictable. For example, Prockop indicates that several different strategies are being pursued for therapeutic use of MSCs and notes that "Obviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy" (p. 74, center column). Similarly, Gerson indicates that many questions need to be addressed regarding the utilization of MSCs in therapeutic regimens (p. 264, left column). Thus, while the teachings indicate that mesenchymal or marrow stromal based therapies appear to be promising, the specific methodologies and clinical efficacy of such therapies remain to be established.

Additionally, transplantation of MSCs in the examples given utilizes autologous or allogeneic sources for the stem cells, as it is well recognized in the art that transplant of xenogeneic cells to a recipient induces a severe immune response, resulting in subsequent loss of transplanted tissue. Saad et al. teach that success of xenotransplantation is confounded by tissue rejection caused by host immune responses. Various factors need to be considered for xenotransplantation, including selection of a donor species and the transplant's compatibility with the recipient, which could induce cellular or humoral rejection (Figure 1, p. 367). Furthermore, they conclude: "thus, it is not possible to predict that xenotransplantation will enter the clinical arena in a very few years (p. 381).

Moreover, at the time of filing, the art of gene therapy was known to be unpredictable and non-routine. Verma et al. indicate that "In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged; problems such as lack of efficient delivery systems, lack of sustained expression, and host

immune response reactions remain formidable challenges; although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story: (p. 239, under Abstract, and left column, paragraphs 1-2).

In view of the lack of teachings or guidance provided by the specification with regard to genetic modification of MSCs and use in gene therapy, and the lack of teachings or guidance provided by the specification to overcome the difficulties and unpredictability of xenogeneic MSC transplantation, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount Of Direction Or Guidance Presented And Working Examples

The specification fails to disclose adequate representations of MSCs that are genetically modified or engineered to contain genes which express proteins of importance for the differentiation and/or maintenance of striated muscle cells (as envisioned on p. 4, lines 15-18 of the instant specification); or the production of MSCs from a xenogeneic source (as stated in line 15, p. 8 of the instant specification). The specification discloses allogeneic MSCs used for transplantation in pig (Examples 4 and 5, p. 15 and 18; and Fig. 3). The specification further describes the implantation of human MSCs into athymic rat myocardial tissue (Example 1, pp. 10-11). However, athymic rats lack the ability to mount an immune response against xenogeneic MSCs. Therefore, Example 1 does not represent a true xenogeneic transplant ot MSCs to cardiac tissue.

The specification provides no additional examples of xenografts or transfer of genetically modified MSCs. The specification does not provide the guidance required to overcome the art-recognized unpredictability of transplant of genetically modified MSCs or xenografts.The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the production of cardiomyocytes by autologous or allogeneic MSCs following transfer of said MSCs to cardiac tissue.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is in possession of the method of administering MSCs from any source, including xenogeneic, or MSCs that are genetically modified, to produce cardiomyocytes in a heart of an individual or improve ventricular wall motion, as claimed in claims 1-2, and 4-10 of the instant application. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level Of Skill In The Art

The level of skill in the art at the time of invention is deemed to be high. However, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Analysis And Summary

Applicant is therefore enabled for a method producing cardiomyocytes in a heart of an individual, comprising: administering to said individual a cardiomyocyte producing amount of autologous or allogeneic MSCs that are not genetically altered. In the instant case, as discussed above, in a highly unpredictable art where the transplantation of xenogeneic MSCs will likely produce a severe immune response and likely lead to tissue rejection, and the lack of knowledge of whether cell and gene therapy is effective in treatment regimens, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise

extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,387,369. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the instant application embraces a method for producing cardiomyocytes in a heart of an individual in need thereof, comprising: administering to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells in at least 20μl and up to about 150 ml of a suspension containing $10\text{-}40\times10^6$ mesenchymal cells/ml. Claim 1 of the 369 patent is directed to a process for producing cardiac muscle cells in the heart of an individual in need thereof, comprising: administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to produce cardiac muscle cells in the heart of said individual, said administered mesenchymal stem cells differentiating into cardiac muscle cells thereby producing cardiac muscle cells in the heart of said individual. The cardiomyocytes of claim 1 of the instant application are synonymous to the cardiac muscle cells of the 369 patent and also embrace autologous or allogeneic mesenchymal stem cells. Further, the specification of the 369 patent states: "multiple injections of 20-50 μl ($10\text{-}40\times10^6$ MSCs/ml) are envisioned. Follow-up therapy may involve additional dosings. In very severe cases, e.g. in a range around the 40% tissue involvement severity level, multiple equivalent doses for a more extended duration with long term (up to several months) maintenance dose aftercare may well be indicated" (third and fourth paragraphs, column 5). As no upper limit for the volume of stem cells is indicated, a volume of up to about 150 ml may be envisioned, as can the

range of 40 ml to 150 ml of claim 2 in the instant application. Claims 3 and 11 are directed to allogenic mesenchymal stem cells, described in claim 1 of the 369 patent.

Claim 4 is directed to improving ventricular wall motion of the heart of an individual. Claim 2 of the 369 patent is drawn to regenerating or repair of cardiac muscle of an individual that has been damaged through disease. Claim 11 of the 369 patent is directed to a process of reducing scar formation in infracted heart tissue. Taken together, claims 2 and 11 of the 369 patent would result in improving ventricular wall motion. This is demonstrated in post-filing art, where transplantation of autologous unmanipulated bone marrow containing MSCs into scarred myocardium of infarcted patients was shown to enhance cardiac function (Galinanes et al., Cell Transplantation 13:7-13; 2004; Title). Galinanes et al. show that following unmanipulated bone marrow stem cell transplantation into damaged myocardium of patients, "only the left ventricle segmental wall motion score of the areas injected with bone marrow and receiving a bypass graft in combination improved" (Abstract).

Claim 5 is directed to direct administration of autologous or allogeneic mesenchymal stem cells to at least one damaged portion of heart tissue. Claim 4 of the 369 patent involves the process of regenerating cardiac muscle that has been damaged through disease, by directly administering mesenchymal stem cells to the heart.

Claim 6 further limits claim 5 to administration by injection, that is also the limitation of claim 6 of the 369 patent.

The limitation of claim 7 involves the administration of autologous or allogeneic mesenchymal stem cells in a pharmaceutically accepatable liquid injectable carrier. To practice the invention of the 369 patent commensurate with the scope of claims 1-10, it would have been obvious to utilize a pharmaceutically acceptable liquid injectable carrier to administer stem cells by injection in a pharmaceutically acceptable carrier, wherein the subject is human (claim7 of the 369 patent).

Claim 8 is drawn to the direct administration of the autologous or allogeneic mesenchymal stem cells during an open surgical procedure. The specification of the 369 patent describes: "under sterile conditions, a 20 mm anterior thoracotomy was performed, and following visualization of the left ventricle, 10 μl of the cell suspension, containing 10,000 to 100,000 MSCs in serum-free medium were injected into the left ventricular apex" (lines 28-33, column 6). The limitation of administration by injection is further covered for claim 9 of the instant application.

Claim 10 is directed to intravenous administration of autologous or allogeneic mesenchymal stem cells to improve ventricular wall motion. Claim 5 of the 369 patent describes systemic administration that encompasses intravenous administration. Furthermore, given that depending on an intended individual subjected to the treatment, e.g., weight, the severity of a need to cardiomycytes, route of administration, it would have been obvious to one of ordinary skill in the art as a matter of design choice or suitability to employ a suitable volume containing a suspenstion containing a sufficient amount of allogeneic or autologous mysenchymal stem cells to the individual, especially since the patent claims clearly claim that so long as an effective amount of aulogous or allogenic mesenchymal stem cells are employed, a desired amount of cardiomycytes shall be produced *in vivo*. Therefore, to practice the invention of the 369 patent, it would have been obvious to utilize the methods claimed in claims 1-11 of the instant application.

Conclusion

No claims allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,435	10/21/2003	Mark F. Pittenger	640100.470	3718

7590 09/22/2006

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ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,435	PITTENGER ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-10 and 12-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of June 26, 2006, to the non-final action dated January 12, 2006 has been entered. Claims 3 and 11 have been cancelled. Claims 1 and 4 have been amended. No claims were newly added. Claims 1-2, 4-10 and 12-21 are pending in the application and under current examination.

Election/Restriction

Upon further consideration, the restriction between Groups I and II, set forth in the office action dated November 3, 2005, is withdrawn and the claims rejoined.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-10 and 12-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 12 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: wherein said administered MSCs differentiate into cardiomyocytes in the heart of said individual, resulting in improved ventricular wall motion of the heart (claims 1 and 4); and wherein said administered MSCs differentiate into blood vessels in the heart of said individual, resulting in repairing or regenerating blood vessels, or promoting angiogenesis in the heart (claims 1 and 4).

Claims 1, 4, 12 and 17 are further unclear. The claims are drawn to methods of producing cardiomyocytes, improving ventricular wall motion, repairing blood vessels and stimulating or promoting angiogenesis in the heart of an individual, by administering (or administering intravenously, in claim 1), an effective amount of MSCs. It is not clear how the administration of MSCs by any route (or intravenously) would produce cardiomyocytes or promote angiogenesis

limited to the heart to an individual. The claims should recite: "administering to the heart of an individual", to be consistent with the preamble of the claims.

New Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 12-21 are newly rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for <u>a method producing cardiomyocytes and improving ventricular wall motion in a heart of an individual, comprising: administering to the heart of said individual a cardiomyocyte producing amount of autologous or allogeneic MSCs, wherein said administered MSCs differentiate into cardiomyocytes in the heart of said individual, resulting in improved ventricular wall motion of the heart,</u> does not reasonably provide an enablement for a method of repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is based on two (2) separate issues: **1)** the absence of an enabling disclosure for the methods of repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to said individual an effective amount of MSCs and **2)** the absence of an enabling disclosure for the aforementioned methods by administering said MSCs from any source, including xenogeneic, or MSCs that are genetically modified, as broadly claimed. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

As a first issue **(1)**, the specification does not provide an enabling disclosure for the methods of repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to said individual an effective amount of MSCs.

The specification states: "Applicants have discovered that the mesenchymal stem cells may stimulate and/or promote angiogenesis in the heart and/or repair or regenerate blood vessel of the heart" (pp. 9-10, bridging). While the engrafted MSCs were found to express numerous muscle specific proteins, and exhibited morphological changes consistent with myogenesis, the specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the heart. The specification discloses human and rat MSCs transplanted to athymic rats (Examples 1-3), and allogeneic MSCs transplanted by direct injection into infracted pig hearts (Examples 4 and 5, p. 15 and 18; and Fig. 3), resulting in improvements in wall motion scores over time (p. 17) as well as cystolic and diastolic wall thickness (p. 18). The specification discloses that the autologous MSCs were isolated from swine bone marrow, expanded in culture, and cryopreserved until the time of transplantation (p. 18). However, no additional information regarding said culture conditions or any additional alterations to the MSCs are provided. Moreover, while the specification discloses that MSCs were identified surrounding and associated with smooth muscle layer of blood vessels (Example 7, p. 20), it remains unknown whether the MSCs contributed to the formation of said blood vessels, as blood vessels were already present in the infracted pig heart.

The post-filing art of Lee et al. (Ann. Intern. Med. 140: 729-737; 2004) in reviewing the status of stem cell transplantation in myocardial infarction, notes that neovascularization is mediated by endothelial progenitor cells stimulated by GCSF (second column, p. 730). Further noting that autologous bone marrow cells secrete angiogenic factors, such as VEGF and macrophage chemoattractant protein 1, that stimulate the proliferation of endothelial cells (first

column, p. 731). The authors conclude that while preliminary data from animal models suggest that infracted myocardium may be regenerated by implanting stem cells, skepticism exists with this treatment method, especially given the initial excitement of angiogenesis studies that did not live up to expectations (second column, p. 735). Therefore, it remains unclear whether transplanted adult MSCs of the instant invention resulted in the repair and regeneration of blood vessels, as even the indirect contribution of the MSCs in providing angiogenesis promoting factors cannot be determined in an environment where such factors are continually supplied by various cells and tissues.

As a second issue **(2)**, the specification does not provide an enabling disclosure for the methods of repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to said individual an effective amount of MSCs from any source, including xenogeneic, or MSCs that are genetically modified.

When given their broadest reasonable interpretation, in view of the as filed specification, claims 11-21 encompass methods of administering MSCs from any source, including cells that are xenogeneic in origin. The specification teaches that the MSCs may be genetically modified or engineered to contain genes which express proteins of importance for differentiation and/or maintenance of striated muscle cells (line 15-17, p. 4). The specification additionally envisions the use of MSCs "in accordance with the invention, in order of preference, autologous, allogeneic or xenogeneic (lines 15-16, p. 8). The specification fails to disclose adequate representations of MSCs that are genetically modified or engineered to contain genes which express proteins of importance for the differentiation and/or maintenance of striated muscle cells (as envisioned on p. 4, lines 15-18 of the instant specification); or the production of MSCs from a xenogeneic source (as stated in line 15, p. 8 of the instant specification). The specification discloses allogeneic MSCs used for transplantation in pig (Examples 4 and 5, pp. 15 and 18; and Fig. 3). The specification further describes the implantation of human MSCs into athymic rat myocardial tissue (Example 1, pp. 10-11). However, athymic rats lack the ability to mount an immune response against xenogeneic MSCs. Therefore, Example 1 does not represent a true xenogeneic transplant of MSCs to cardiac tissue.

The specification provides no additional examples of xenografts or transfer of genetically modified MSCs. The specification does not provide the guidance required to overcome the art-recognized unpredictability of transplant of genetically modified MSCs or xenografts.

The state of the prior art with regard to transplantation of MSCs and gene therapy are effectively summarized by the references of Prockop (Science 276:71-74, 1997; of record); Gerson, S. (Nature Medicine 5:262-264, 1999; of record); Saadi et al. (Life Sciences 62:365-387, 1998); and Verma et al. (Nature 389:239-242, 1997, of record).

The prior art at the time of filing suggests that MSC transplantation and *in vivo* therapeutic effectiveness have not been established such that utilizing these cells to treat diseases, disorders, or conditions is routine or predictable. For example, Prockop indicates that several different strategies are being pursued for therapeutic use of MSCs and notes that "Obviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy" (p. 74, center column). Similarly, Gerson indicates that many questions need to be addressed regarding the utilization of MSCs in therapeutic regimens (p. 264, left column). Thus, while the teachings indicate that mesenchymal or marrow stromal based therapies appear to be promising, the specific methodologies and clinical efficacy of such therapies remain to be established.

Additionally, transplantation of MSCs in the examples given utilizes autologous or allogeneic sources for the stem cells, as it is well recognized in the art that transplant of xenogeneic cells to a recipient induces a severe immune response, resulting in subsequent loss of transplanted tissue. Saadi et al. teach that success of xenotransplantation is confounded by tissue rejection caused by host immune responses. Various factors need to be considered for xenotransplantation, including selection of a donor species and the transplant's compatibility with the recipient, which could induce cellular or humoral rejection (Figure 1, p. 367). Furthermore, they conclude: "thus, it is not possible to predict that xenotransplantation will enter the clinical arena in a very few years (p. 381).

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the production of cardiomyocytes by autologous or allogeneic MSCs following transfer of said MSCs to cardiac tissue.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to MSCs from any source, including xenogeneic, or MSCs that are genetically modified, to repair or regenerate blood vessels or to stimulate or promote angiogenesis, as claimed in the instant application.

Therefore, in view of the art recognized high level of unpredictability where the transplantation of xenogeneic MSCs will likely produce a severe immune response and likely lead to tissue rejection, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification regarding the contribution of MSCs to repair or regeneration of blood vessels, or promoting angiogenesis, it is the position of the examiner that it would require undue experimentation for one of skill in the art to practice the scope of the invention as broadly claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Response to Obviousness Type Double Patenting

Claims 1-11 were previously rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,387,369, in the office action dated January 12, 2006. In view of the terminal disclaimer filed June 26, 2006, the previous rejection is withdrawn.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(703) 272-**

3311. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,435	10/21/2003	Mark F. Pittenger	640100.470	3718

7590 03/22/2007

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,435	PITTENGER ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 26 December 2006.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/24/06 & 1/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Applicants' response of December 26, 2006, to the non-final action dated September 22, 2006 has been entered. Claims 1, 4, 12 and 17 have been amended. No claims were cancelled or newly added. Claims 1-2, 4-10 and 12-21 are pending in the application and under current examination.

New Claim Objection under 37 CFR § 1.121

Claims 1 and 4 are newly objected to, under 37 CFR § 1.121 (c) for containing incorrect status identifiers. Claims 1 and 4 are currently amended, but have been identified as (Previously presented). Appropriate correction of the claim status identifiers is required.

Applicants should note that the submission of any further defective amendments will results in a notice of non-compliant amendment.

Claims 16 and 21 are newly objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 16 and 21 depend from claims 12 and 17 respectively and recite that the mesenchymal stem cells are allogeneic, thus failing to further limit the base claims.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1-2, 4-10 and 12-21 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The rejection set forth on pp. 2-3 of the previous office action dated September 22, 2006 is maintained in part for claims 1-2, 4-10 and 12-21 for reasons of record. Applicants' amendment of claims 1, 4, 12 and 17, adding essential steps, partially obviates the previous ground of rejection.

Applicants disagree with the rejection, asserting that the specification states that mesenchymal stem cells (MSCs) can be administered by a variety of procedures and Lee et al. (of record) state that "Transplanted stem cells also undergo a "homing" process in which they are

attracted to the site of injury" [column 2, lines 26-28], and those skilled in the art, when reading the specification, would understand readily that, if administered systemically, the mesenchymal stem cells will travel to the heart in order to produce cardiomyocytes or blood vessels of the heart, thereby improving ventricular wall motion, repairing or regenerating blood vessels, or stimulating or promoting angiogenesis in the heart. Applicants' arguments have been fully considered, but are not found persuasive.

The issue is how the administration of MSCs by any route (or intravenously) would produce cardiomyocytes or promote angiogenesis limited to the heart to an individual. For example, an intradermal delivery of MSCs is unlikely to produce cardiomyocytes in the heart.

Regarding systemic or intravenous administration (claim 1), it appears that the teachings of Lee et al. are taken out of context. Lee et al. teach that regeneration of cardiomyocytes may be attained by mobilizing bone marrow resident stem cells to the site of injury with the use of cytokines such as granulocyte colony stimulating factor, by a homing mechanism that is not clearly understood, (second column, p. 729), or by an indirect approach where MSCs which were mobilized by systemic injections of cytokines (such as GMCSF and stem-cell factor) homed to the infracted myocardium (pp. 729-730, bridging). The instant claims are not directed to bone marrow resident stem cells and further do not recite the mobilization of MSCs by systemic injections of cytokines.

It is therefore maintained that the claims should recite: "administering to the heart of an individual", to be consistent with the preamble of the claims.

Thus, the rejection of claims 1-2, 4-10 and 12-21 is maintained for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 12-21 stand rejected under 35 U.S.C.§112, first paragraph, because the specification lacks an enablement for the full scope of the claimed invention. The rejection set forth on pp. 3-7 of the previous office action dated September 22, 2006 is maintained in party for claims 12-21, for reasons of record. Applicants' amendment of claims 12 and 17, identifying MSCs as autologous or allogeneic, partially obviates the previous ground of rejection.

Applicants traverse the rejection, asserting the examples show that MSCs did contribute to the formation of blood vessels in the heart. Referring to Examples 6 and 7 of the specification, Applicants state that MSCs were found surrounding, and associated with blood vessels of the heart. The MSCs were localized within a blood vessel, and associated with the smooth muscle layer of the vessel and expressed Factor VIII and VEGF. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it is maintained that the specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the heart. Localization and association with the smooth muscle layer is not synonymous with repair or regeneration of blood vessels or the promotion of angiogenesis, as the amount or sufficiency of the expressed factors cannot be determined. Therefore, it remains unclear whether transplanted adult MSCs of the instant invention resulted in the repair and regeneration of blood vessels, as even the indirect contribution of the MSCs in providing angiogenesis promoting factors cannot be determined in an environment where such factors are continually supplied by various cells and tissues.

Applicants cite *Ex parte Mark*, and argue that Applicants need not show that every embodiment within the scope of a claim must be operable in order for the claim to be valid. Such is not persuasive, because the subject matter in *Ex parte Mark* was directed to cysteine-depleted muteins of biologically active proteins and is thus not on point. Further, the allogeneic MSCs in Example 7 were transplanted by direct injection into infracted pig hearts, and not administered by other means. Additionally, the working example does provide an enablement for formation of blood vessels or angiogenesis, and moreover, a single embodiment does not overcome the art recognized unpredictability for the genus encompassed by the claims. As also indicated in MPEP 2164.03, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938).

Therefore, it is maintained that the specification does not provide an enabling disclosure for repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis in the heart of an individual, or where MSCs (or genetically modified MSCs) are administered by any route to said individual.

Thus, the rejection of claims 1-2, 5-13, 22-27 and 49-57 is maintained for reasons of record and the foregoing discussion.

Conclusion

Claims 1-2, 4-10 and 12-21 are not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633
FGS

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

I/W

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JUN 2 5 2007
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Examining Operations

Applicant(s):	Pittenger, *et al.*		
Serial No:	10/690,435		
Filed:	October 21, 2003		
Title:	Cardiac Muscle Regeneration Using Mesenchymal Stem Cells		
Examiner:	Sajjadi	Art Unit:	1633
Attorney Docket No.:	640100 - 470	Customer No.	27162

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

SIR:

Enclosed please find the following:

1. Amendment; and
2. A self-addressed, postage paid, return receipt postcard, the date stamp and return of which is respectfully requested.

The Commissioner is authorized to charge payment of any additional filing fees required under 37 C.F.R. §1.16 associated with this communication or credit any overpayment to Deposit Account **No. 03-0678.**

FIRST CLASS CERTIFICATE

I hereby certify that this correspondence is being deposited today with the U.S. Postal Service as First Class Mail in an envelope addressed to:

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Raymond J. Lillie — 6/20/07

Raymond J. Lillie — **Date**

Respectfully submitted,

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#320922 v1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Pittenger, et al.
Serial No.:	10/690,435
Filed:	October 21, 2003
For:	Cardiac Muscle Regeneration Using Mesenchymal Stem Cells
Group:	1633
Examiner:	Sajjadi

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

AMENDMENT

A. INTRODUCTORY REMARKS

This is an Amendment in response to the Final Rejection dated March 22, 2007.

B. AMENDMENTS TO THE CLAIMS

1. (Previously presented) A method for producing cardiomyocytes in a heart of an individual, comprising:

administering intravenously to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells in at least 20 μl and up to about 150 μl of a suspension containing 10-40 x 10^6 mesenchymal stem cells/ml, wherein said administered mesenchymal stem cells differentiate into cardiomyocytes.

2. (Original) The method of Claim 1 wherein said individual is administered from 40 ml to 150 ml of a suspension containing 10-40 x 10^6 mesenchymal stem cells/ml.

Claim 3 is cancelled without prejudice.

4. (Previously presented) A method of improving ventricular wall motion of the heart of an individual, comprising:

administering to said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells, wherein said administered mesenchymal stem cells differentiate into cardiomyocytes, thereby improving ventricular wall motion of the heart of said individual.

5. (Original) The method of Claim 4 wherein said mesenchymal stem cells are administered directly to at least one damaged portion of heart tissue.

6. (Original) The method of Claim 5 wherein the mesenchymal stem cells are administered by injection.

7. (Original) The method of Claim 6 wherein the mesenchymal stem cells are administered in a pharmaceutically acceptable liquid injectable carrier.

8. (Original) The method of Claim 5 wherein the mesenchymal stem cells are administered during an open surgical procedure.

9. (Original) The method of Claim 8 wherein the mesenchymal stem cells are administered by injection.

10. (Original) The method of Claim 4 wherein the mesenchymal stem cells are administered intravenously.

Claim 11 has been canceled without prejudice.

12. (Previously presented) A method of repairing or regenerating blood vessels of the heart of an individual, comprising:

administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to repair or regenerate blood vessels in the heart of said individual, wherein said administered mesenchymal stem cells differentiate into blood

vessels in the heart of said individual, thereby repairing or regenerating blood vessels of the heart of said individual.

13. (Original) The method of Claim 12 wherein said mesenchymal stem cells are administered directly to the heart.

14. (Original) The method of Claim 13 wherein said mesenchymal stem cells are administered by injection.

15. (Original) The method of Claim 14 wherein the mesenchymal stem cells are administered in a pharmaceutically acceptable liquid injectable carrier.

16. (Original) The method of Claim 12 wherein said mesenchymal stem cells are allogeneic to the individual.

17. (Previously presented) A method of stimulating or promoting angiogenesis in the heart of an individual, comprising:

administering to said individual autologous or allogeneic mesenchymal stem cells in an amount effective to stimulate or promote angiogenesis in the heart of said individual, wherein said administered mesenchymal stem cells differentiate into blood vessels in the heart of said individual, thereby promoting angiogenesis in the heart of said individual.

18. (Original) The method of Claim 17 wherein said mesenchymal stem cells are administered directly to the heart.

19. (Original) The method of Claim 18 wherein said mesenchymal stem cells are administered by injection.

20. (Original) The method of Claim 19 wherein said mesenchymal stem cells are administered in a pharmaceutically acceptable liquid injectable carrier.

21. (Original) The method of Claim 17 wherein said mesenchymal stem cells are allogeneic to the individual.

22. (New). A method of improving ventricular wall motion of the heart of an individual, comprising:

administering to said individual autologous or allogeneic mesenchymal stem cells, wherein said mesenchymal stem cells are administered into an amount effective to improve ventricular wall motion of the heart of said individual.

23. (New). The method of Claim 22 wherein said mesenchymal stem cells are administered directly to at least one damaged portion of heart tissue.

24. (New). The method of Claim 23 wherein the mesenchymal stem cells are administered by injection.

25. (New). The method of Claim 24 wherein the mesenchymal stem cells are

administered in a pharmaceutically acceptable liquid injectable carrier.

26. (New). The method of Claim 23 wherein the mesenchymal stem cells are administered during an open surgical procedure.

27. (New). The method of Claim 26 wherein said mesenchymal stem cells are administered by injection.

28. (New). The method of Claim 22 wherein the mesenchymal cells are administered intravenously.

C. REMARKS

Claims 22-28 have been added in order to define an additional aspect of the present invention.

Claims 16 and 21 stand objected to under 37 CFR 1.121. This objection is respectfully traversed.

The Examiner has taken the position that Claims 16 and 21 do no not limit further the independent claims upon which they depend, i.e., Claims 12 and 17, respectively. Claims 12 and 17 are directed to repairing or regenerating blood vessels of the heart (Claim 12) or stimulating or promoting angiogenesis in the heart (Claims 17) of an individual by administering autologous or allogeneic mesenchymal stem cells. Each of Claims 16 and 21 define the mesenchymal stem cells as allogeneic mesenchymal stem cells. Therefore, contrary to the Examiner's assertions, Claims 16 and 21 limit further independent Claims 12 and 17, respectively, upon which they depend. It is therefore respectfully requested that the objection under 37 CFR 1.121 be reconsidered and withdrawn.

Claims 1, 2, 4-10 and 12-21 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The Examiner has taken the position that it is unlikely that the administration of mesenchymal stem cells by means other than administration to the heart of an individual would produce cardiomyocytes or promote angiogenesis in the heart.

The Examiner is reminded that all that is required by 35 U.S.C. 112, second paragraph, is that the claims point out particularly and claim distinctly the subject matter sought to be patented. (See In Re Borkowski, 164 U.S. P.Q. 642 (C.C.P.A. 1970), at 645.) Applicants and only Applicants are the first to produce cardiomyocytes in the heart, improve ventricular wall motion of the heart or stimulate or promote angiogenesis in the heart of an individual by administering autologous or allogeneic mesenchymal stem cells.

It is clear that Applicants are claiming a method of producing cardiomyocytes in a heart, improving ventricular wall motion of the heart, or stimulating or promoting angiogenesis in the heart of an individual by administering autologous or allogeneic mesenchymal stem cells. Applicants have not indicated that they intend the claims to be of a different scope. Thus, the claims point out particularly and claim distinctly the subject matter that Applicants regard as the invention. (Id., at 645 – 646.)

As in Borkowski, the Examiner cannot study Applicants' disclosure, and then determine whether Applicants' claims are broader than the Examiner's conception of what "the invention" is. (See Borkowski, supra, at 645.) Section 112 does not permit such an approach to claims. Id.

In sum, Applicants have pointed out particularly and claimed distinctly the subject matter that they regard as the invention. It is not within the prerogative of the Examiner to conclude or hold that only a specific means of administration of the mesenchymal stem cells can be included in the claim in order for such claim to comply with 35 U.S.C. 112, second paragraph. In that the claims particularly point out and claim distinctly the subject matter Applicants regard as the invention, the claims are patentable under 35 U.S.C. 112, second paragraph. It is therefore respectfully requested that the rejection under 35 U.S.C. 112 second paragraph, be reconsidered and withdrawn.

Claims 12-21 stand rejected under 35 U.S.C. 112, first paragraph, because the specification lacks an enablement for the full scope of the claimed invention. This rejection is respectfully traversed.

The Examiner has taken the position that the specification does not provide an enabling disclosure for repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis in the heart of an individual, or where mesenchymal stem cells are administered by any route to said individual.

The Examiner admits that Examples 6 and 7 state that mesenchymal stem cells were found surrounding, and associated with blood vessels of the heart. The Examiner, however, believes that such localization and association is not synonymous with repair or regeneration of blood vessels or the promotion of angiogenesis.

In Example 7, at Page 20, Applicants state that mesenchymal stem cells were associated with the smooth muscle layer of a blood vessel, and that such cells expressed Factor VIII and VEGF. As stated at Page 20, Factor VIII and VEGF are not expressed by cultured mesenchymal stem cells, but are expressed only after several weeks in the cardiac environment. Thus, contrary to the Examiner's assertions, Applicants have demonstrated that the mesenchymal stem cells did contribute to the formation of blood vessels in the heart.

The Examiner also takes the position that Applicants have demonstrated only the direct injection of mesenchymal stem cells to the heart, and have not demonstrated that administration of the mesenchymal stem cells by other means would be successful.

As noted hereinabove, Applicants have demonstrated that one can administer mesenchymal stem cells to the heart, and that such mesenchymal stem cells contribute to the formation of blood vessels in the heart. Thus, Applicants have proven the principle that one can repair or regenerate blood vessels in the heart by administering mesenchymal stem cells. The Examiner has provided no evidence, other than sheer speculation, that methods of administration other than direct administration of the mesenchymal stem cells to the heart would not be effective in repairing or regenerating blood vessels in the heart. The Examiner therefore, has not met his burden in showing that methods of administration, other than direct administration of the mesenchymal stem cells to the heart, would not be enabled. Thus for the above reasons and others, Claims 12-21 are enabled in accordance with 35 U.S.C. 112, first paragraph, and it is

therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

Raymond J. Lillie

Raymond J. Lillie
Registration No. 31,778

#314569 v1

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,435	10/21/2003	Mark F. Pittenger	640100.470	3718

7590 07/17/2007

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/690,435	**Applicant(s)** PITTENGER ET AL.	
	Examiner Fereydoun G. Sajjadi	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *16 and 21*.
   Claim(s) rejected: *1-10 and 12-28*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Advisory Action

Continuation of 11. does NOT place the application in condition for allowance because:

The objection to claims 16 and 21, as failing to further limit the subject matter of claims 12 and 17, respectively, is maintained for reasons of record. Claims 12 and 17 recite "autologous or allogeneic". Autologous cells are derived from the same individual and allogeneic cells are derived from the same species. Therefore the recitation of "allogeneic" in dependent claims 16 and 21 is broader than the limitation of "autologous", as a species encompasses more than one individual.

The examiner maintains the rejection of claims 1, 2, 4-10 and 12-21 under 35 USC 112, second paragraph. Applicants' argument that it is clear that what is claimed is a method of producing cardiomyocytes in a heart, improving ventricular wall motion of the heart or stimulating or promoting angiogenesis in the heart of the individual, is not found persuasive. While the intended use of the methods is to produce cardiomyocytes, or repair or regenerate blood vessels in the heart, the language contained in the body of the claim makes it unclear whether the cardiomyocytes are actually produced in the heart or elsewhere in the body. That the claims recite "administering to the heart of an individual" should only be considered a suggestion, as to clarify the claim language at issue.

The rejection of claims 12-21 under 35 USC 112, first paragraph, scope of enablement, is maintained for reasons of record. Applicants argue that Example 7 states that MSCs are associated with the smooth muscle layer of a blood vessel and that such cells expressed factor VIII and VEGF, not expressed in clultured MSCs; concluding that the MSCS did contribute to the formation of blood vessels in the heart Such is not persuasive, because such a conclusion would be premature in view of the fact that the specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the heart. Localization and association with the smooth muscle layer is not synonymous with repair or regeneration of blood vessels or the promotion of angiogenesis, as the amount or sufficiency of the expressed factors cannot be determined. The association of the MSCs may be with blood vessels already present in the heart tissue. Therefore, it remains unclear whether transplanted adult MSCs of the instant invention resulted in the repair

and regeneration of blood vessels, as even the indirect contribution of the MSCs in providing angiogenesis promoting factors cannot be determined in an environment where such factors are continually supplied by various cells and tissues.

In response to Applicants' argument that the Examiner has provided no evidence, other than sheer speculation, that methods of administration other than direct administration of the MSCs to the heart would not be effective in repairing or regenerating blood vessels in the heart, it should be noted that the enabled scope previously indicated in the office action of 9/22/2006 did not indicate an enablement for MSC mediated "repairing or regenerating blood vessels in the heart", regardless of the route of administration. Furthermore, the instant claims have been examined in accordance with the *Wands* factors, and in view of the teachings of the post-filing art of record, the high level of unpredictability in transplantation and differentiation of MSCs, and the lack of guidance provided by the specification, it is concluded that the specification does not enable a person of skill in the art to make and use the invention without undue experimentation. Therefore, it is maintained that the specification does not provide an enabling disclosure for repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis in the heart of an individual, or where MSCs (or genetically modified MSCs) are administered by any route to said individual. Thus, the rejection of claims 12-21 is maintained for reasons of record and the foregoing discussion.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Fereydoun G. Sajjadi, Ph.D.
Examiner
Art Unit 1633

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633

XI. RELATED PROCEEDINGS APPENDIX

None.